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Influence of Pretransplantation Restrictive Lung Disease on Allogeneic Hematopoietic Cell Transplantation Outcomes

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We conducted a 15-year retrospective cohort study to determine the prevalence of restrictive lung disease before allogeneic hematopoietic cell transplantation (HCT), and to assess whether this was a risk factor for poor outcomes. A total of 2545 patients were eligible for the analysis. Restrictive lung disease was defined as a total lung capacity (TLC) < 80% of predicted normal. Chest x-rays and /or computed tomography (CT) scans were reviewed for all restricted patients to determine whether lung parenchymal abnormalities were unlikely or highly likely to cause restriction. Multivariate Cox proportional hazard and sensitivity analyses were performed to assess the relationship between restriction and early respiratory failure and nonrelapse mortality. Restrictive lung disease was present in 194 subjects (7.6%) before HCT. Among these cases, radiographically apparent abnormalities were unlikely to be the cause of the restriction in 149 subjects (77%). In unadjusted and adjusted analyses, the presence of pulmonary restriction was significantly associated with a 2-fold increase in risk for early respiratory failure and nonrelapse mortality, suggesting that these outcomes occurring in the absence of radiographically apparent abnormalities may be related to respiratory muscle weakness. These findings suggest that pulmonary restriction should be considered a risk factor for poor outcomes after transplantation.

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KEY WORDS: Pulmonary restriction, Allogeneic hematopoietic cell transplantation, Survival, Mortality risk

INTRODUCTION

Pulmonary function tests (PFTs) are routinely performed before allogeneic hematopoietic cell transplantation (HCT) to screen for underlying respiratory abnormalities and to provide baseline lung function measurements for comparison when transplantation-related pulmonary complications are suspected [1]. Several studies examining the predictive value of pretransplantation PFTs for posttransplantation complications have demonstrated that impaired lung function before transplantation increases the risk for posttransplantation pulmonary complications and mortality [2-14]. However, the majority of these previous studies focused primarily on the 1-second forced expiratory volume (FEV_1) [2,12,14] and the carbon monoxide diffusion capacity (DLCO) [10-12,14] as a surrogate measure of pulmonary gas exchange, or on the effect of specific physiological patterns, such as the effect of pretransplantation airflow obstruction, on posttransplantation outcome [3,4,9,12]. Although a few studies have evaluated the relationship between pretransplantation pulmonary restriction and posttransplantation outcomes [2,12,15], the prevalence of restrictive lung disease before allogeneic HCT and its influence on transplantation outcome have not been well described.

Multiple factors can result in a restrictive pattern on pulmonary function testing before HCT, including advanced intrathoracic malignant lesions, spinal cord compression, prior treatments (eg, chemotherapy,

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thoracic surgery, thoracic radiation), prior chronic respiratory disease or infection, and/or myopathies/deconditioning resulting in respiratory muscle weakness [1]. In a recent study, we found evidence that a reduced total lung capacity (TLC), which defines pulmonary restriction, before allogeneic HCT may influence posttransplantation outcome [8]. These preliminary data and the current gap in knowledge regarding restrictive pulmonary processes and allogeneic HCT outcomes prompted us to conduct a 15-year retrospective cohort study to determine the prevalence of restrictive lung disease before allogeneic HCT, and to assess whether this is a pretransplantation risk factor for 2 major transplantation outcomes: early respiratory failure and nonrelapse mortality (NRM).

METHODS

Patient Selection

All patients who underwent a first allogeneic HCT at Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance (the "Center") between July 6, 1992, and July 6, 2005, were eligible for this analysis (n = 2847). Patients under age 15 years (n = 170), and those without a pretransplantation assessment of pulmonary static lung volume (n = 132), were excluded. A total of 2545 patients were included in the final analyses.

Clinical Data

All clinical data were prospectively collected and retrospectively reviewed. The patient's underlying disease state was categorized as low risk, intermediate risk, or high risk, as described previously [8,16]. Donor match status was determined according to donor–recipient ABO compatibility and HLA-A, -B, and -DR status. Stem cell sources were classified as bone marrow (BM), peripheral blood stem cell (PBSC), other (including cord blood [CB]), or a combination of BM and PBSC. Conditioning regimens were classified as reduced intensity (RIC) or myeloablative (MA). Patients in the MA conditioning group included patients that received either a total body irradiation (TBI)- or non–TBI-based regimen. Patients in the RIC group received 2 Gy of TBI. Body mass index (BMI) was calculated using weight and height and categorized as underweight (BMI < 18.5), normal weight (BMI 18.5-24.9), overweight (BMI 25.0-29.9), or obese (BMI > 30.0) [17].

Pulmonary Function Testing

According to standard transplantation protocol at our Center, all patients underwent pulmonary function testing before transplantation when possible. The PFT values obtained before and closest to the time of transplantation were used in the analysis. In those patients who received a bronchodilator challenge, the prebronchodilator values were used. All PFTs were performed at our Center according to the American Thoracic Society (ATS) guidelines [18] using a Sensormedics 2100 (Sensormedics, Yorba Linda, CA) between July 1991, and August 1999, and a Sensormedics V-Max 22 with Autobox 6200 between September 1999, and July 2005. Published equations for adults were used to determine predicted values of FEV_1, forced vital capacity (FVC), TLC, residual volume (RV), and DLCO [18-20]. All DLCO measurements were corrected for the hemoglobin measurement obtained closest to the time of measurement of diffusion capacity, but not alveolar volume [21].

Chest Imaging

Chest imaging data were reviewed for all patients determined to have pretransplantation restrictive lung disease by PFT results. Data were obtained by reviewing chest x-ray and computed tomography (CT) reports when available, and by reviewing clinical notes when imaging reports were not available. Imaging was performed within 30 days before or after HCT in the majority of the subjects (96%). When both chest x-ray and chest CT results were available within the same time window, CT results were used preferentially. All reports were independently and collectively reviewed by 3 pulmonologists and classified as having either a high probability or a low probability that parenchymal lung disease or chest wall deformities were contributing significantly to the restrictive lung disease. Nodules, lobar infiltrates, cavities < 4 cm in size, and small effusions were classified as low probability. Evidence of thoracic surgery, elevated diaphragm, diffuse interstitial lung disease, pulmonary fibrosis, central masses, and moderate to severe pleural effusions were classified as high probability.

Restrictive Pulmonary Disease Definitions

Restrictive lung disease was defined according to ATS/European Respiratory Society (ERS) criteria as a TLC $< 80\%$ (definition 1) [20,22]. To examine the possible association between respiratory muscle weakness and outcome, we performed a sensitivity analysis using 2 additional definitions of restrictive lung disease. The first definition required both a TLC $< 80\%$ and a FEV_1/FVC ratio > 0.7 (definition 2). The second alternative definition required the same, as well as a low-probability chest image that provided no evidence of a parenchymal explanation for the restrictive pattern (definition 3).

Outcome Definitions

Patients were considered to have developed early respiratory failure if they required $>$ 24 hours of

mechanical ventilation for a nonelective reason within the first 120 days after HCT. NRM was defined as mortality in patients who did not experience relapse of their underlying malignancy during the follow-up period.

Statistical Methods

All statistical analyses were performed using SPSS 15.0 for Windows (SPSS, Chicago, IL) and Stata/IC 10.0 for Windows (StataCorp, College Station, TX). Two-sided P values $\leq .05$ were considered statistically significant. Diagnosis, disease status, and disease risk were evaluated as categorical variables. PFT parameters and BMI were evaluated as both continuous and categorical variables. Pearson's χ^2 test and one-way analysis of variance were used to compare categorical and continuous variables, respectively. To evaluate a possible association between respiratory muscle weakness and worse outcome, we performed a sensitivity analysis using 3 successively more stringent definitions for a restrictive pattern likely caused by respiratory muscle weakness. Cox proportional hazards models were used to assess the relationship between pulmonary restriction and the outcomes of interest. Patients who experienced disease relapse were censored at the time of relapse for the NRM analysis. To account for potential changes in clinical practice over time, the year of transplantation was considered a categorical variable in the analysis. The incidence of developing early respiratory failure and NRM according to lung function parameters were plotted using cumulative incidence curves, with disease relapse treated as a competing event for NRM and all-cause mortality treated as a competing event for respiratory failure. Cumulative incidence curves were compared using the method of Gray [25].

RESULTS

Clinical Characteristics and Baseline Lung Function

Table 1 summarizes pretransplantation clinical characteristics of all patients. The mean (± standard deviation) number of days between pulmonary function testing and transplantation was 24 ± 9 days. Restrictive lung disease, defined as a TLC < 80%, was present in 194 patients (7.6%) (Table 2). The prevalence of restrictive lung disease increased with increasing disease risk ($P < .001$; Table 3), from 4% in low-risk patients to 7% in intermediate-risk patients and 12% in high-risk patients. A total of 107 chest x-rays and 81 chest CT scans were reviewed for the 194 patients with a restrictive pattern. Six patients did not have any radiographic images available for review. The majority of patients with a TLC < 80% had normal or near-normal chest radiographic findings (n = 149; 77%) and were categorized as having a low likelihood of parenchymal lung disease or a chest wall deformity being a cause of pulmonary restriction. The remainder of the patients with a TLC < 80% (n = 39; 20%) had prior thoracic surgery or radiographic evidence of a mediastinal, lung, or pleural abnormality and were classified as having a high likelihood of parenchymal lung disease or a chest wall deformity being a significant cause of pulmonary restriction. Patients with the most severely diminished TLC were more likely to have abnormal chest imaging results (31% vs 5%; $P < .001$).

Table 1. Patient Pretransplantation Characteristics

Characteristic	n (%) or Mean ± SD
Total number of patients	2545 (100)
Age at transplantation, years	42 ± 12.3
White race	2141 (84.1)
Male sex	1487 (58.4)
Donor type	
HLA-matched related	1690 (66.4)
HLA-mismatched related	565 (22.2)
Unrelated	237 (9.3)
Conditioning regimen	
Myeloablative	2338 (92)
Nonmyeloablative	207 (8)

Among pretransplantation characteristics, only disease diagnosis and stage were significantly associated with a TLC < 80% (Table 3). Although the majority of the patients were in the highest TLC category, a larger percentage of those with Hodgkin disease (HD) had a pretransplantation TLC in the lowest category ($P < .001$). Similarly, there also was a significant association between baseline TLC and disease status at transplantation ($P < .001$). To facilitate further analysis, we integrated the pretransplantation diagnosis and disease status into a composite variable—disease risk—and confirmed the association with pretransplantation TLC (Table 3). Because physiological deconditioning or pulmonary injury from significant pretreatment can result in a restrictive pattern and influence the risk of developing the outcome, disease risk represents a potential confounding variable. Because of the low number of patients in each TLC category below 80%, we also dichotomized the TLC categories into ≥ 80% versus < 80% for the remaining analyses.

Pretransplantation Restrictive Lung Disease and Early Respiratory Failure

Pretransplantation restrictive lung disease was significantly associated with a higher risk of early respiratory failure (hazard ratio [HR] = 2.22; 95% confidence interval [CI] = 1.60-3.07; $P < .001$) (Table 4). The cumulative incidence of early respiratory failure was significantly different between patients with a pretransplantation TLC < 80% and those with

Table 2. Distribution of PFT Parameters and Chest Imaging Findings According to Pretransplantation TLC Category

	Pretransplantation TLC Category				
	≥ 80%	70%-79%	60%-69%	< 60%	*P* Value*
Number of patients (%)	2351 (92.4)	134 (5.3)	39 (1.5)	21 (0.8)	
Mean BMI (± SD)	27 ± 5	28 ± 6	26 ± 5	23 ± 4	.010
Mean percent of predicted (± SD)					
FEV_1	94 ±13	74 ± 9	61 ± 11	53 ± 20	<.0001
FVC	100 ±13	75 ± 9	63 ± 12	55 ± 21	<.0001
FEV_1/FVC ratio	0.77 ± 0.07	0.80 ± 0.05	0.80 ± 0.06	0.82 ± 0.07	<.0001
RV	100 ± 26	76 ± 17	76 ± 19	76 ± 28	<.0001
DL_{CO}	90 ±17	74 ±20	62 ±13	54 ± 16	<.0001
Chest radiographic findings†					
Low probability	NA	113 (76)	29 (19)	7 (5)	<.0001
High probability	NA	18 (46)	9 (23)	12 (31)	<.0001

NA indicates not available; PFT, pulmonary function test; TLC, total lung capacity; DLCO, carbon monoxide diffusion capacity; FEV1, 1-second forced expiratory volume; FVC, forced vital capacity; RV, residual volume.
*The Pearson χ^2 test and one-way analysis of variance were used to compare categorical and continuous variables, respectively.
†Six patients did not have radiologic data available for review.

a pretransplantation TLC ≥ 80% ($P < .0001$) (Figure 1A). In an attempt to isolate the effect of respiratory muscle weakness, we repeated this analysis using progressively stringent criteria for restrictive lung disease. When restrictive lung disease was defined as both a TLC < 80% and an FEV_1/FVC ratio > 0.7, it remained significantly associated with a 2-fold increase in risk for early respiratory failure (HR = 2.19; 95% CI = 1.57-3.06; $P < .001$). Using these criteria for pulmonary restriction, the cumulative incidence of early respiratory failure remained significantly different between patients with and without pretransplantation pulmonary restriction ($P < .0001$) (Figure 1B). The third analysis required a TLC < 80%, an FEV_1/FVC ratio > 0.7, and a low-probability chest radiograph. Although attenuated slightly, a restrictive pattern remained significantly associated with an increased risk of early respiratory failure (HR = 1.84; 95% CI = 1.25-2.71; $P < .002$). Even under this definition of pulmonary restriction, patients with and without pretransplantation pulmonary restriction still had a significantly different cumulative incidence of early respiratory failure ($P = .012$) (Figure 1C).

Given the potentially confounding effects of disease risk, we repeated these analyses after adjusting for disease risk in the models. We also adjusted for year of transplantation to account for any changes in clinical practice over the duration of the study. These adjustments reduced the point estimates; however, the associations between pulmonary restriction and early

Table 3. Distribution of Diagnosis, Disease Status, and Disease Risk According to Pretransplantation TLC Category

		Pretransplantation TLC Category				
	Total	≥80%, n (%)	70%-80%, n (%)	60%-70%, n (%)	<60%, n (%)	*P* Value*
Diagnosis						<.001
Chronic myelogenous leukemia	810	770 (95)	30 (4)	8 (1)	2 (<1)	
Acute myelogenous leukemia	747	695 (93)	39 (5)	10 (1)	3 (<1)	
Myelodysplastic syndrome	446	410 (92)	24 (5)	9 (2)	3 (<1)	
Acute lymphocytic leukemia	261	230 (88)	21 (8)	7 (3)	3 (1)	
Non-Hodgkin lymphoma	147	129 (88)	7 (5)	2 (1)	4 (3)	
Multiple myeloma	64	55 (86)	5 (8)	2 (8)	2 (3)	
Chronic lymphocytic leukemia	50	46 (92)	3 (6)	0 (0)	1 (2)	
Hodgkin disease	25	15 (60)	6 (24)	1 (4)	3 (12)	
Disease status						<.001
Accelerated phase	139	132 (95)	5 (4)	1 (<1)	1 (<1)	
Blast crisis	92	80 (87)	8 (9)	3 (3)	1 (<1)	
Chronic phase	581	560 (96)	17 (3)	4 (<1)	0 (0)	
De novo	34	30 (88)	1 (2)	3 (10)	0 (0)	
Relapse	607	534 (88)	47 (8)	11 (2)	15 (2)	
Remission	591	555 (94)	27 (5)	8 (1)	1 (<1)	
Unknown	43	39 (91)	4 (9)	0 (0)	0 (0)	
Other	459	420 (92)	27 (6)	9 (2)	3 (<1)	
Disease risk						<.001
Low	724	693 (96)	23 (3)	8 (1)	0 (0)	
Intermediate	995	926 (93)	50 (5)	15 (1)	4 (<1)	
High	808	715 (88)	61 (8)	15 (2)	17 (2)	

TLC indicates total lung capacity.
*Pearson's χ^2 test was used to compare categorical variables.

Table 4. Sensitivity Analysis of the Association between Pretransplantation Restriction and Early Respiratory Failure

	n (%)	Events	Unadjusted HR (95% CI)	Unadjusted *P* Value	Adjusted* HR (95% CI)	Adjusted* *P* Value
TLC < 80%						
No	2351 (92)	261	—		—	
Yes	194 (8)	43	2.22 (1.60-3.07)	< .001	1.90 (1.36-2.65)	< .001
TLC < 80% + FEV_1/FVC > 0.7						
No	2358 (93)	263	—		—	
Yes	185 (7)	41	2.19 (1.57-3.06)	< .001	1.90 (1.35-2.66)	< .001
TLC < 80% + FEV_1/FVC > 0.7 + low-probability chest imaging						
No	2396 (93)	275	—		—	
Yes	143 (6)	28	1.84 (1.25-2.71)	.002	1.59 (1.07-2.37)	.022

TLC indicates total lung capacity; FEV1, 1-second forced expiratory volume; FVC, forced vital capacity.
*Adjusted for disease risk and year.

respiratory failure remained statistically significant for the first 2 definitions, and a trend toward significance with a smaller effect size remained for the third definition (Table 4).

Because of fundamental differences in characteristics among patients receiving an MA conditioning regimen and those receiving a nonmyeloablative (NMA) conditioning regimen, we also stratified the adjusted analysis based on this criterion. Among patients who received a MA conditioning regimen (n = 2338), the presence of pretransplantation pulmonary restriction remained significantly associated with increased risk for early respiratory failure in the adjusted analysis (definition 1: HR = 1.67, 95% CI = 1.43-1.95, $P < .001$; definition 2: HR = 1.68, 95% CI = 1.43-1.96, $P < .001$; definition 3: HR = 1.46, 95% CI = 1.44-1.98, $P < .001$). Among patients who received an RIC regimen (n = 207), the presence of pretransplantation pulmonary restriction according to definitions 1 and 2 was associated with an increased risk of early respiratory failure. This difference was no longer statistically significant in adjusted analyses (definition 1: HR = 2.81, 95% CI = 0.73-10.82, $P = .134$; definition 2: HR = 1.80, 95% CI = 0.38-8.46, $P = .455$). There was an insufficient number of cases with definition 3 to allow an informative analysis.

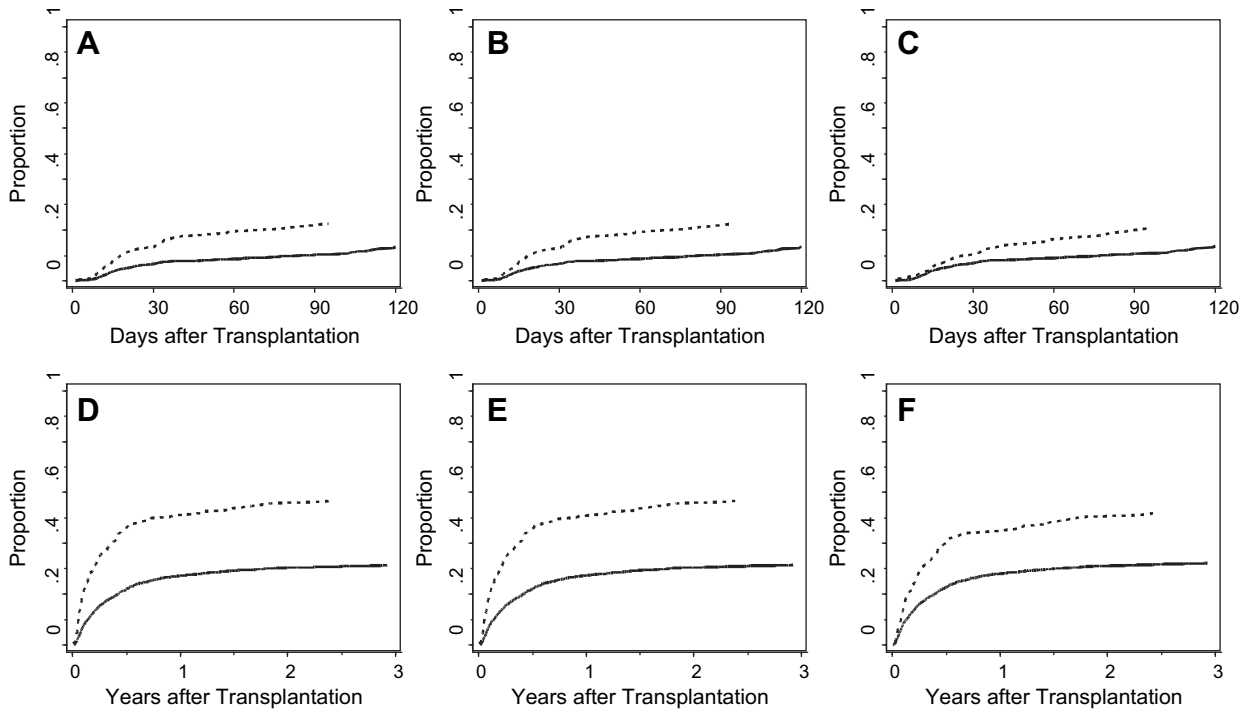

Figure 1. Cumulative incidence curves for early respiratory failure (A, B, and C) and NRM (E, F, and G). The dotted lines indicate patients with pretransplantation pulmonary restriction; the solid lines, patients without pretransplantation pulmonary restriction. Three definitions of pretransplantation pulmonary restriction were used: TLC< 80% alone (A and D), TLC < 80% and FEV_1/FVC ratio > 0.7 (B and E), TLC < 80%, FEV_1/FVC ratio > 0.7, and a low-probability chest radiograph (C and F). Gray's test indicates significant differences between patients with and without pulmonary restriction in cumulative incidence of early respiratory failure (A, $P < .000$; B, $P < .0001$; C, $P = .012$) and cumulative incidence of NRM (D, $P < .0001$; E, $P < .0001$; F, $P < .0001$).

Pretransplantation Restrictive Lung Disease and NRM

Restrictive lung disease also was significantly associated with an increased risk of NRM (HR = 2.41; 95% CI = 1.98-2.94; $P < .001$) (Table 5). Sensitivity analyses using the alternative definitions revealed that the association remained significant. According to definition 2, the presence of a restrictive pattern was associated with a 2-fold increase in the risk of NRM (HR = 2.39; 95% CI = 1.95-2.92; $P < .001$). According to definition 3, the presence of a restrictive pattern was still significantly associated with a 2-fold increase in the risk of NRM (HR = 1.98; 95% CI = 1.57-2.50; $P < .001$). Using each of the 3 definitions of pulmonary restriction, the cumulative incidence of NRM was significantly different between patients with and without pulmonary restriction ($P < .0001$) (Figure 1D, E, and F).

We also repeated these analyses after adjusting for disease risk and year of transplantation in the models. The resultant point estimates were decreased slightly, but the association between pulmonary restriction and nonrelapse mortality remained statistically significant for all 3 definitions of pulmonary restriction (Table 4). We also performed stratified analyses of the adjusted models based on conditioning regimen. Among patients who received an MA conditioning regimen, the presence of pretransplantation pulmonary restriction remained significantly associated with increased risk of NRM (definition 1: HR = 2.07, 95% CI = 1.68-2.56, $P < .001$; definition 2: HR = 2.10, 95% CI = 1.70-2.60, $P < .001$; definition 3: HR = 1.74, 95% CI = 1.37-2.22, $P < .001$). Among patients who received an RIC regimen, the association with NRM was neither consistent nor statistically significant with each definition for pretransplantation pulmonary restriction (definition 1: HR = 1.69, 95% CI = 0.86-3.32, $P = .125$; definition 2: HR = 1.18, 95% CI = 0.55-2.56, $P = .669$; definition 3: HR = 0.59, 95% CI = 0.17-2.04, $P = .404$).

DISCUSSION

Evaluation of pulmonary function serves as an important method for risk stratification of patients who are considering allogeneic HCT [7,8,10,23-25]. The most recent studies clearly indicate that the presence of poor lung function before HCT is associated with worse outcomes, including respiratory failure and mortality [7,24]. But, these studies, along with many others, are limited in their ability to comment on the potential biological mechanisms by which poor lung function might influence a patient's posttransplantation clinical course. The literature contains 2 possible explanations for these repeated observations: (1) Impaired lung function likely leaves a patient with less pulmonary reserve, meaning less lung capacity for surviving a period of critical illness, and (2) previous lung injury may have immunologically primed the lungs, predisposing the lungs to additional immunologic injury during the transplantation process. Based on the observations of our current analysis, we suspect that there may be a third explanation linked to pulmonary restriction and respiratory muscle weakness.

Pretransplantation pulmonary restriction is a significant clinical problem. In the current study, we found that the prevalence of pulmonary restriction among transplantation candidates was only 8%, which is much lower than a previously reported prevalence of 29% in a study of patients who underwent transplantation between 1984 and 1990, an entirely different era of stem cell transplantation [2,12,15]. Given the observations associated with our most stringent definition of pulmonary restriction, we suspect that the majority of these patients with pulmonary restriction (77%) likely had evidence of respiratory muscle weakness before transplantation. This supposition is supported by 2 observations. First, there was a direct correlation between BMI and TLC values; patients with lower BMI, who may be more likely to be physiologically deconditioned because poor nutritional status, had lower TLC values. Second, there also was a significant relationship between disease type/risk and the degree of TLC reduction. Although this could indicate that patients with the most advanced disease were more likely to have had thoracic or pulmonary injury resulting in pulmonary restriction, patients who had radiographic evidence of parenchymal or thoracic abnormalities

Table 5. Sensitivity Analysis of the Association between Pretransplantation Restriction and Nonrelapse Mortality

			Unadjusted		Adjusted*	
	n (%)	Events	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
TLC < 80%						
No	2351 (92)	261	—		—	
Yes	194 (8)	43	2.41 (1.98-2.94)	< .001	2.18 (1.79-2.65)	<.001
TLC < 80% + FEV1/FVC > 0.7						
No	2358 (93)	263	—		—	
Yes	185 (7)	41	2.39 (1.95-2.92)	< .001	2.18 (1.78-2.66)	<.001
TLC < 80% + FEV1/FVC > 0.7 + low-probability chest imaging						
No	2396 (93)	275	—		—	
Yes	143 (6)	28	1.98 (1.57-2.50)	< .001	1.82 (1.44-2.30)	<.001

*Adjusted for disease risk and year.

that could cause restrictive lung disease were in the minority. Instead, we believe that this group of patients were most likely to be physiologically deconditioned because of multiple previous rounds of aggressive cancer treatment. Based on these observations, our results go beyond confirming that the presence of pulmonary restriction before transplantation was associated with a higher risk of respiratory failure and NRM. Our study provides the first published evidence that pretransplantation pulmonary restriction may be caused by respiratory muscle weakness. This may partially explain the well-established relationship between poor lung function and worse allogeneic HCT outcome.

Our analysis accounted for the major variables that could influence pulmonary function. First, as clearly demonstrated by the significant relationship between disease risk and pretransplantation pulmonary restriction, we included disease risk as a potential confounding variable. Whereas this inclusion attenuated the magnitude of the effect associated with pretransplantation pulmonary restriction, we demonstrated that despite this adjustment, this relationship with the two outcomes remained statistically significant. Second, we also accounted for potential changes in patient selection over the course of the 14-year study period by including the year of transplantation in our models. Again, this did not significantly influence our results, suggesting that this relationship is durable despite temporal changes related to transplantation procedures and patient selection. Third, recognizing the potential physiological differences in the patient populations receiving MA versus RIC regimens, we stratified our analyses accordingly, and found that although the association remained strong in patients who received an MA regimen, it was less so for those who received an RIC regimen. Nevertheless, we note that, at least for the respiratory failure endpoint, the point estimates for the RIC patients were similar in magnitude to those observed among the MA patients. Our cohort may have been underpowered to demonstrate statistical significance for the RIC patients with respect to mortality.

Our study is subject to the usual limitations associated with single-center retrospective studies. In addition, perhaps the study's most noteworthy limitation is the lack of data from direct measurements of respiratory muscle strength with such tools as maximum inspiratory and expiratory pressures, or even indirectly with grip strength. We were only able to infer that a restrictive pattern noted on PFTs, in the absence of any radiographic features that may explain the restrictive pattern, was most likely attributable to respiratory muscle weakness. However, respiratory muscle dysfunction is often present before pulmonary restriction is apparent on PFTs [26-28], suggesting that we have most likely underestimated the prevalence of respiratory muscle dysfunction. Although data for respiratory muscle strength are not available in our database, we believe that such measurements not only could contribute significantly to our understanding of this process, but also help direct clinical care with interventions that can increase respiratory muscle strength. Future prospective studies should consider incorporating relatively simple tools for measuring respiratory muscle function (eg, maximum inspiratory and expiratory pressures), which are available through most pulmonary function testing laboratories, to evaluate patients with and without a pretransplantation TLC $< 80\%$.

In summary, the results from the current study demonstrate that pretransplantation restrictive lung disease is a risk factor for allogeneic HCT outcomes and possibly may be attributable to respiratory muscle weakness. This may partially explain the higher risk for poor transplantation outcome that has long been associated with poor pretransplantation lung function. If this is confirmed, future studies should consider evaluating interventions aimed at strengthening respiratory muscles to determine whether such measures can improve the outcomes of allogeneic HCT.

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